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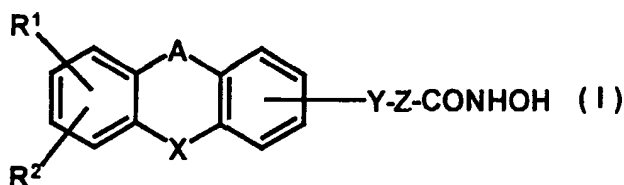
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WO 02/085883 A1

(54) Title: TRICYCLIC ALKYLHYDROXAMATES, THEIR PREPARATION AND THEIR USE AS CELL PROLIFERATION INHIBITORS



(57) Abstract: Compounds of formula (I), wherein R<sub>1</sub>, R<sub>2</sub>, A, X, Y and Z have the meanings defined in the specification, process of manufacturing these compounds and pharmaceuticals with HDAC inhibitor activity containing such a compound.

## TRICYCLIC ALKYLHYDROXAMATES, THEIR PREPARATION AND THEIR USE AS CELL PROLIFERATION INHIBITORS

The invention relates to tricyclic alkylhydroxamate derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-cell-proliferation activity such as anti-cancer activity and are accordingly useful in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said tricyclic alkylhydroxamate derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of an anti-cell-proliferation effect in a warm-blooded animal such as man.

### Background of the invention

Transcriptional regulation is a major event in cell differentiation, proliferation, and apoptosis. Transcriptional activation of a set of genes determines cell destination and for this reason transcription is tightly regulated by a variety of factors. One of its regulatory mechanisms involved in the process is an alteration in the tertiary structure of DNA, which affects transcription by modulating the accessibility of transcription factors to their target DNA segments. Nucleosomal integrity is regulated by the acetylation status of the core histones. In a hypoacetylated state, nucleosomes are tightly compacted and thus are nonpermissive for transcription. They are relaxed by acetylation of the core histones, with the result being permissiveness to transcription. The acetylation status of the histones is governed by the balance of the activities of histone acetyl transferase (HAT) and histone deacetylase (HDAC). Recently, HDAC inhibitors have been found to arrest growth and apoptosis in several types of cancer cells, including colon cancer, T-cell lymphoma, and erythroleukemic cells. Given that apoptosis is a crucial factor for cancer progression, HDAC inhibitors are promising reagents for cancer therapy as effective inducers of apoptosis (Koyama, Y., et al., Blood 96 (2000) 1490-1495).

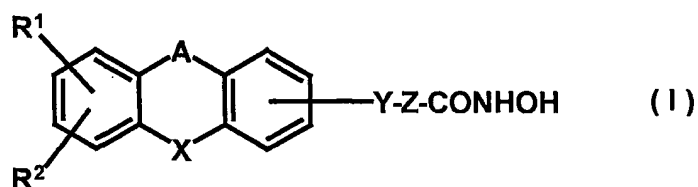
Several structural classes of HDAC inhibitors have been identified and are reviewed in Marks, P.M., et al., Journal of the National Cancer Institute 92 (2000) 1210-1216. More specifically, WO 98/55449 (by The University of Queensland et al, "Hydroxamic Acid Compounds Having Anticancer And Anti-Parasitic

Properties”), and US 5,369,108 (by Breslow, R., et al., “Potent Inducers Of Terminal Differentiation And Methods Of Use Thereof”) report alkanoyl hydroxamates with HDAC inhibitory activity.

5 We have now found that certain tricyclic alkylhydroxamate derivatives possess anti-cell-proliferation properties which are more potent than those in the aforementioned references. These properties are due to HDAC inhibition.

### Description of the invention

10 According to the invention there is provided a tricyclic alkylhydroxamate derivative of the formula I



wherein

- 15 A denotes a bond, the groups  $-\text{CH}_2-\text{O}-$ ,  $-\text{CH}_2-\text{S}-$ ,  $-\text{CH}_2-\text{CH}_2-$ , or  $-\text{NH}-\text{CO}-$ ;
- X denotes the group  $-\text{NR}^3-$ ,  $=\text{CO}$ , or  $-\text{CH}(\text{OH})-$ ;
- Y denotes an oxygen atom, a sulfur atom, or the group  $-\text{NR}^4-$ ;
- 20 Z denotes a straight chain alkylene group comprising 4, 5, 6, 7, or 8 carbon atoms, wherein one  $\text{CH}_2$  group may be replaced by an oxygen or a sulfur atom, or wherein 2 carbon atoms form a  $\text{C}=\text{C}$  double bond, and which is either unsubstituted or substituted by one or two substituents selected from (1-4C)alkyl and halogen atoms;
- 25  $\text{R}^1$  and  $\text{R}^2$  denote substituents independently selected from a hydrogen atom, halogen atoms, (1-4C)alkyl, trifluoromethyl, hydroxy, (1-4C)alkoxy, benzyloxy, (1-3C)alkylenedioxy, nitro, amino, (1-4C)alkylamino, di[(1-4C)alkyl]-amino, or (1-4C)alkanoylamino groups;
- $\text{R}^3$  and  $\text{R}^4$  independently denote hydrogen atoms or (1-4C)alkyl groups;

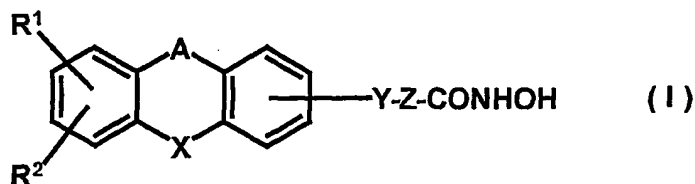
their enantiomers, diastereoisomers, racemates, salts and mixtures thereof.

A suitable value for a substituent when it is a halogen atom is, for example, fluoro, chloro, bromo and iodo; when it is (1-4C)alkyl is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl; when it is (1-4C)alkoxy is, for example, methoxy, ethoxy, propoxy, isopropoxy or butoxy; when it is (1-4C)alkylamino is, for example, methylamino, ethylamino or propylamino; when it is di-[(1-4C)alkyl]amino is, for example, dimethylamino, N-ethyl-N-methylamino, diethylamino, N-methyl-N-propylamino or dipropylamino; when it is (1-4C)alkanoylamino is, for example, formylamido, acetamido, propionamido or butyramido; and when it is (1-3C)alkylenedioxy is, for example, methylenedioxy, ethylenedioxy or propylenedioxy.

Preferred tricycles of formula I are dibenzoxepine, dibenzazepine, fluorene or carbazol.

Y is preferred an oxygen atom. Z is a straight chain alkylene group with 4 to 8 carbon atoms, preferably 4 to 7. The chain can be substituted by one or two halogen atoms, preferably chlorine, or a C<sub>1</sub>-C<sub>4</sub>-alkyl group, preferably methyl. One -CH<sub>2</sub>-group of the chain can be replaced by an oxygen or sulfur atom, however, this group should not be the first or last member of the chain. A CH<sub>2</sub>-CH<sub>2</sub>-group of the chain can also form a -CH = CH-group.

Preferred compounds of the invention include tricyclic alkylhydroxamate derivatives of the formula I



wherein

- |    |   |   |
|----|---|---|
| 25 | A | denotes a bond, the groups -CH <sub>2</sub> -O-, or -NH-CO-;            |
|    | X | denotes the group -NR <sup>3</sup> -, =CO, or -CH(OH)-;                 |
|    | Y | denotes an oxygen atom, a sulfur atom, or the group -NR <sup>4</sup> -; |

- 4 -

Z denotes a straight chain alkylene group comprising 4, 5, 6, 7, or 8 carbon atoms, wherein one CH<sub>2</sub> group may be replaced by an oxygen or a sulfur atom, or wherein 2 carbon atoms form a C=C double bond, and which is either unsubstituted or substituted by one or two substituents selected from (1-4C)alkyl and halogen atoms;

R<sup>1</sup> and R<sup>2</sup> denote substituents independently selected from halogen atoms, (1-4C)alkyl, trifluoromethyl, hydroxy, (1-4C)alkoxy, benzyloxy, (1-3C)alkylenedioxy, nitro, amino, (1-4C)alkylamino, di[(1-4C)alkyl]amino, or (1-4C)alkanoylamino groups;

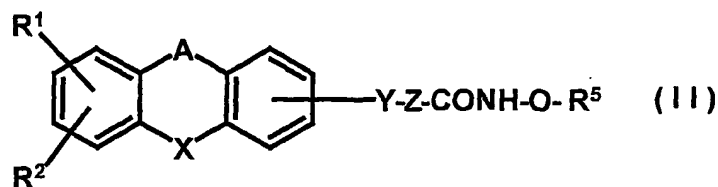
R<sup>3</sup> and R<sup>4</sup> independently denote hydrogen atoms or (1-4C)alkyl groups;

their enantiomers, diastereoisomers, racemates, salts and mixtures thereof.

#### Preparation of the Compounds of the Invention

A tricyclic alkylhydroxamate derivative of the formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a tricyclic alkylhydroxamate derivative of the formula I, or a pharmaceutically-acceptable salt thereof, are provided as a further feature of the invention and are illustrated by the following representative examples in which, unless otherwise stated, A, X, Y, Z, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> have any of the meanings defined hereinbefore. The starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting examples. Alternatively starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skills of an organic chemist.

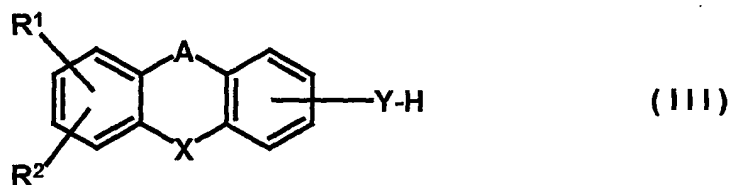
(a) One preferred method for the preparation of compounds of the formula I is the deprotection of compounds of the formula II



wherein  $R^5$  is a suitable protecting group. Compounds of the formula II are new and included in the present invention.

Suitable protecting groups are the benzyl-, p-methoxybenzyl-, tert.butyloxycarbonyl-, trityl-, or silyl groups such as the trimethylsilyl- or dimethyl-tert.butylysilyl-group. The reactions carried out depend on the type of the protecting group. When the protecting group is a benzyl- or p-methoxybenzyl group, the reaction carried out is a hydrogenolysis in an inert solvent such as an alcohol like methanol or ethanol, in the presence of a noble metal catalyst such as palladium on a suitable carrier such as carbon, barium sulfate, or barium carbonate, at ambient temperature and pressure. When the protecting group is the tert.butyloxycarbonyl-, trityl-, or a silyl group such as the trimethylsilyl- or dimethyl-tert.butylysilyl-group, the reaction is carried out in the presence of acids at a temperature between  $-20^{\circ}\text{C}$  and  $60^{\circ}\text{C}$ , preferably between  $0^{\circ}\text{C}$  and ambient temperature. The acid may be a solution of hydrochloric acid in an inert solvent such as diethyl ether or dioxane, or trifluoro acetic acid in dichloromethane. Alternatively, when the protecting group is a silyl group such as the trimethylsilyl or dimethyl-tert.butylysilyl group, the reaction is carried out in the presence of a fluoride source such as sodium fluoride or tetrabutyl ammonium fluoride in an inert solvent such as dichloromethane.

Compounds of the formula II are obtained by the reaction of a tricyclic alkylhydroxamate of the formula III



with a compound of formula IV



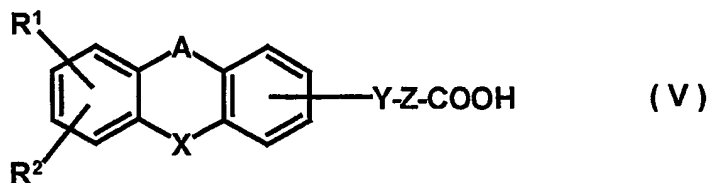
wherein W is a displaceable group and Z and  $R^5$  have the meaning defined hereinbefore, in the absence or presence of a suitable base.

A suitable displaceable group W is, for example, a halogeno, or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-p-sulphonyloxy group. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alkanol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The reaction is conveniently carried out at a temperature in the range, for example, 10 to 250°C, preferably in the range 40-200°C.

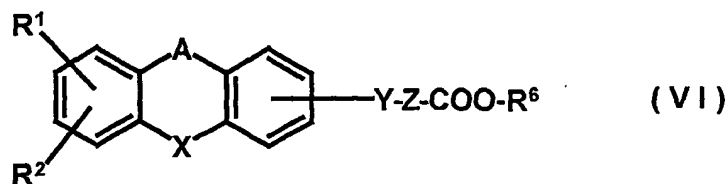
The compounds of the general formula III are either commercially available or can be prepared according to the following literature references or in analogous manners. Compounds of the formula III wherein A denotes a bond and X denotes the group  $\text{NR}^3$ -, can be prepared according to the German Patent Application DE 2928483 (Lauer, K., and Kiegel, E.; Boehringer Mannheim GmbH). Compounds of the formula III wherein A denotes a bond, the group  $-\text{CH}_2\text{CH}_2-$ , or  $-\text{CH}_2-\text{O}-$  and X denotes the group  $=\text{CO}$ -, can be prepared according to the German Patent Application DE 2208893 (Winter, W., et al.; Boehringer Mannheim GmbH).

(b) Another preferred method for the preparation of compounds of the formula I involves the reaction of compounds of the formula V



with hydroxylamine. This reaction typically involves a two-step one-pot procedure. In the first step, the carboxylate of the formula V becomes activated. This reaction is carried out in an inert solvent or diluent, for example, in dichloromethane, dioxane, or tetrahydrofuran, in the presence of an activating agent. A suitable  
 5 reactive derivative of an acid is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid with an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol  
 10 such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate or an alcohol such as methanol, ethanol, isopropanol, butanol or N-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of the acid and a cyanide such as  
 15 diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as dicyclohexylcarbodiimide. The reaction is carried out between -30°C and 60°C, conveniently at or below 0°C. In the second step, hydroxylamine is added to the solution, at the temperature used for the activation, and the temperature is slowly adjusted to ambient temperature.

20 Compounds of the formula V are prepared from compounds of the formula VI

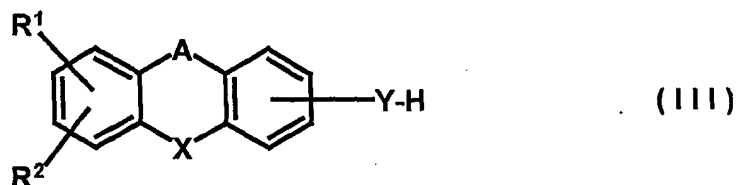


wherein  $R^6$  is an alkyl group, for example, a methyl, ethyl, or tert. butyl group or benzyl group, by hydrolysis. The conditions under which the hydrolysis is carried out depend on the nature of the group  $R^6$ . When  $R^6$  is a methyl or ethyl group, the  
 25 reaction is carried out in the presence of a base, for example, lithium hydroxide, sodium hydroxide, or potassium hydroxide in an inert solvent or diluent, for example, in methanol or ethanol. When  $R^6$  is the tert.butyl group, the reaction is carried out in the presence of an acid, for example, a solution of hydrochloric acid in an inert solvent such as diethyl ether or dioxane, or trifluoro acetic acid in



dichloromethane. When  $R^6$  is the benzyl group, the reaction is carried out by hydrogenolysis in the presence of a noble metal catalyst such as palladium on a suitable carrier, such as carbon.

Compounds of the formula VI are prepared from compounds of the formula III



5

by reaction with compounds of the formula VII

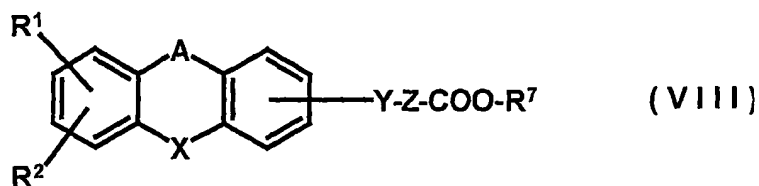


in the presence of a suitable base.

10 A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

15 The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alkanol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or  
20 dimethylsulfoxide. The reaction is conveniently carried out at a temperature in the range, for example, 10 to 250°C, preferably in the range 40-200°C.

(c) A third preferred method for the production of compounds of the formula I involves the reaction of compounds of the formula VIII



wherein  $R^7$  is an (1-4C)alkyl group, for example, a methyl or ethyl group, with hydroxylamine in the presence of a suitable base.

5 The reaction is carried out in an inert solvent or diluent such as methanol or ethanol at temperatures between  $0^{\circ}\text{C}$  and  $100^{\circ}\text{C}$ , conveniently at or near ambient temperature, and at a pH between 9 and 11. A suitable base is, for example, an alcoholate, for example, sodium methylate.

10 (d) Those compounds of the formula I wherein one of the substituents is an amino group may be prepared by the reduction of a derivative of the formula I wherein the substituent is a nitro group. The reduction may conveniently be carried out by any of the many procedures known for such a transformation. The reduction may be carried out, for example, by the hydrogenation of a solution of the nitro compound in an inert solvent or diluent as defined hereinbefore in the presence of a suitable metal catalyst such as palladium or platinum. A further  
15 suitable reducing agent is, for example, an activated metal such as activated iron (produced by washing iron powder with a dilute solution of an acid such as hydrochloric acid). Thus, for example, the reduction may be carried out by heating a mixture of the nitro compound and the activated metal in a suitable solvent or diluent such as a mixture of water and an alcohol, for example, methanol or  
20 ethanol, to a temperature in the range, for example,  $50$  to  $150^{\circ}\text{C}$ , conveniently at or near  $70^{\circ}\text{C}$ .

25 (e) Those compounds of the formula I wherein X denotes the  $-\text{CH}(\text{OH})-$  group may be prepared by the reduction of a derivative of the formula I wherein X denotes the  $=\text{CO}$  group. The reduction may conveniently be carried out by any of the many procedures known for such a transformation. The reduction may be carried out, for example, by hydrogenation in an inert solvent or diluent as defined hereinbefore in the presence of a suitable metal catalyst such as palladium or

platinum, for example, in methanol or ethanol, at a temperature in the range, for example, 0 to 100°C, conveniently at or near ambient temperature.

(f) Those compounds of the formula I wherein one of the substituents is an (1-4C)alkanoylamino group, are prepared by acylation of a derivative of the formula I wherein the substituent is an amino group. A suitable acylating agent is, for example, any agent known in the art for the acylation of amino to acylamino, for example an acyl halide, for example an alkanoyl chloride or bromide, conveniently in the presence of a suitable base, as defined hereinbefore, an alkanoyl acid anhydride or mixed anhydride, for example acetic anhydride or the mixed anhydride formed by the reaction of an alkanoyl acid and an alkoxycarbonyl halide, for example an alkoxycarbonyl chloride, in the presence of a suitable base as defined hereinbefore. In general the acylation is carried out in a suitable inert solvent or diluent as defined hereinbefore and at a temperature, in the range, for example, -30 to 120°C, conveniently at or near ambient temperature.

The enantiomers or diastereoisomers of the compounds of formula I can be obtained by usual methods as column chromatography or crystallization or optical resolution of enantiomers by treatment with optically active acids or bases or by using optically active starting materials.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a tricyclic alkylhydroxamate derivative of the formula I, or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier. The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. In general the above compositions may be prepared in a manner using conventional excipients. The tricyclic alkylhydroxamate will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be

varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

5 According to a further aspect of the present invention there is provided a tricyclic alkylhydroxamate derivative of the formula I as defined hereinbefore for use in a method of treatment of the human or animal body by therapy. We have now found that the compounds of the present invention possess anti-cell-proliferation properties which are believed to arise from their histone deacetylase inhibitory activity. Accordingly the compounds of the present invention provide a method for  
10 treating the proliferation of malignant cells. Accordingly the compounds of the present invention are expected to be useful in the treatment of cancer by providing an anti-proliferative effect, particularly in the treatment of cancers of the breast, lung, colon, rectum, stomach, prostate, bladder, pancreas and ovary. It is in addition expected that a derivative of the present invention will possess activity  
15 against a range of leukemias, lymphoid malignancies and solid tumors such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas.

Thus according to this aspect of the invention there is provided the use of a tricyclic alkylhydroxamate derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the  
20 production of an anti-cell-proliferation effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-cell-proliferation effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said  
25 animal an effective amount of a tricyclic alkylhydroxamate derivative as defined hereinbefore.

The anti-cell-proliferation treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compounds of the invention, one or more other anti-tumor substances, for example those selected from, for example,  
30 mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; inhibitors of microtubule assembly, like paclitaxel or other taxanes; antimetabolites, for example 5-fluorouracil,

capecitabine, cytosine arabinoside and hydroxyurea, or, for example, intercalating antibiotics, for example adriamycin and bleomycin; immunostimulants, for example trastuzumab; DNA synthesis inhibitors, e.g. gemcitabine; enzymes, for example asparaginase; topoisomerase inhibitors, for example etoposide; biological  
5 response modifiers, for example interferon; and anti-hormones, for example antioestrogens such as tamoxifen or, for example antiandrogens such as (4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl) - propionanilide, or other therapeutic agents and principles as described in, for example, Cancer: Principles & Practice of Oncology, Vincent T. DeVita, Jr., Samuel  
10 Hellmann, Steven A. Rosenberg; 5<sup>th</sup> Ed., Lippincott-Raven Publishers, 1997. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of individual components of the treatment. According to this aspect of the invention there is provided a pharmaceutical product comprising a tricyclic alkylhydroxamate derivative of the formula I as defined hereinbefore and an  
15 additional anti-tumor substance as defined hereinbefore for the conjoint treatment of cancer.

The invention will now be illustrated in the following non-limiting examples in which, unless otherwise stated:

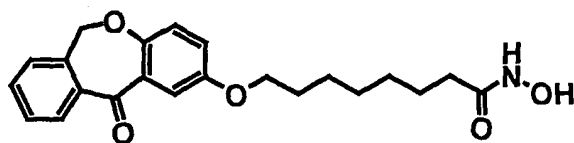
- 20 (i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;
- (ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;
- 25 (iii) column chromatography (by the flash procedure) and high pressure liquid chromatography (HPLC) were performed on Merck Kieselgel silica or Merck Lichroprep RP-18 reversed-phase silica obtained from E. Merck, Darmstadt, Germany;
- (iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) melting points were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Kofler hot plate apparatus.

(vi) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques (Micromass Platform II machine using APCI or Micromass Platform ZMD using electrospray);

(vii) intermediates were not generally fully characterized and purity was assessed by thin layer chromatography.

### Example 1



8-(11-Oxo-6,11-dihydro-dibenzo[b,e]oxepin-2-yloxy)-octanoic acid hydroxyamide

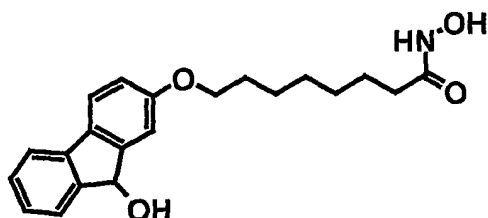
(a) In an ice bath, 14 ml triethylamine was added to a suspension of 3.2 g (20 mmol) O-benzylhydroxylamine hydrochloride in 150 ml dichloromethane. Stirring was continued until the solution became clear. Then, 4.5 g (20 mmol) omega-bromo octanoic acid was added, followed by 5.6 g (22 mmol) bis-(2-oxo-3-oxazolidinyl)-phosphorylchloride. Stirring was continued at ambient temperature for 18 h. The solution was extracted twice with 150 ml each of 1M aqueous hydrochloric acid and twice with 150 ml each of 1M aqueous sodium bicarbonate. The organic solvent was removed i. vac. to give 5.1 g (78%) of 8-bromo-octanoic acid benzyloxy-amide as a colorless oil. MS: 330 ( $M+H^+$ ).

(b) 488mg (3.5 mmol) Potassium carbonate was added to a solution of 400 mg (1.8 mmol) 2-hydroxy-6H-dibenzo[b,e]oxepin-11-one and 580 mg (1.8 mmol) 8-bromo-octanoic acid benzyloxy-amide in dimethyl formamide. The slurry was heated to 100 °C for 14h. After cooling to ambient temperature, water was added and extracted with ethyl acetate. The organic phase was washed with water, dried

over sodium sulfate, filtered, and the solvent was evaporated. The residue was purified by column chromatography using ethyl acetate / heptane 1:1 as eluent. There was thus obtained 420mg (50%) ) 8-(11-Oxo-6,11-dihydro-dibenzo[b,e]oxepin-2-yloxy)-octanoic acid benzyloxyamide as a colorless oil. MS: 474 (M+H<sup>+</sup>); 472 (M-H<sup>+</sup>).

(c) 400 mg (0.845 mmol) 8-(11-Oxo-6,11-dihydro-dibenzo[b,e]oxepin-2-yloxy)-octanoic acid benzyloxyamide in 50 ml methanol was hydrogenated in the presence of palladium on calcium carbonate at ambient temperature and pressure. The catalyst was removed by filtration and the solvent was evaporated. The residue was purified by column chromatography (methanol / water 75:25). There was thus obtained 90 mg (28%) of the title compound as an amorphous solid. MS: 382 (M-H<sup>+</sup>); 384 (M+H<sup>+</sup>).

### Example 2



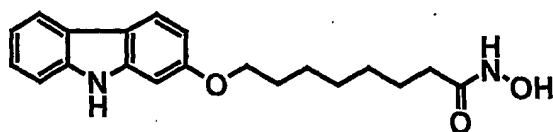
*rac*-8-(9-Hydroxy-9H-fluoren-2-yloxy)-octanoic acid hydroxyamide

(a) In a manner analogous to that of example 1(b), 8-bromo-octanoic acid benzyloxy-amide (example 1(a); 0.3 g, 1.3 mmol) was reacted with 2-hydroxy-fluoren-9-one (0.30 g, 1.5 mmol) in the presence of potassium carbonate (0.21 g, 1.5 mmol) and dimethyl formamide (10 ml) to give 8-(9-oxo-9H-fluoren-2-yloxy)-octanoic acid benzyloxyamide as an almost colorless wax (yield 0.43 g, 63%; purified by column chromatography using silica gel and ethyl acetate : heptane = 1 : 1 as eluent). MS (M-H<sup>+</sup>) = 442.

(b) In a manner analogous to that of example 1(c), 8-(9-oxo-9H-fluoren-2-yloxy)-octanoic acid benzyloxyamide (430 mg, 1 mmol) was hydrogenated to give

the title compound (160 mg) in 46% yield as an amorphous solid. MS ( $M-H^+$ ) = 354.

Example 3



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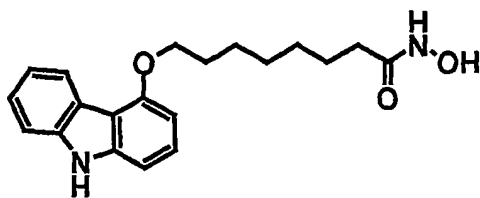
8-(9H-Carbazol-2-yloxy)-octanoic acid hydroxyamide

(a) In a manner analogous to that of example 1(b), 8-bromo-octanoic acid benzyloxy-amide (example 1(a); 0.3 g, 1.1 mmol) was reacted with 2-hydroxy-9H-carbazol (0.3 g, 1.1 mmol) in the presence of potassium carbonate (0.15 g, 1.1 mmol) and DMF as solvent to give 8-(9H-carbazol-2-yloxy)-octanoic acid benzyloxyamide as an almost colorless wax (yield 0.1 g, 20%; purified by column chromatography using silica gel and ethyl acetate as eluent). MS ( $M+H^+$ ) = 483.

(b) In a manner analogous to that of example 1(c), 8-(9H-carbazol-2-yloxy)-octanoic acid benzyloxyamide (90 mg, 430 mmol) in tetrahydrofuran was hydrogenated in the presence of palladium on barium sulfate to give the title compound as a crystalline solid (16 mg). MS ( $M-H^+$ ) = 339.

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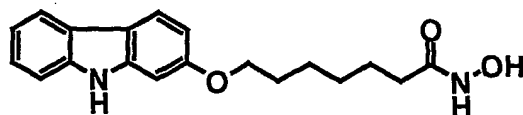


Example 4

## 8-(9H-Carbazol-4-yloxy)-octanoic acid hydroxyamide

(a) In a manner analogous to that of example 1(b), 8-bromo-octanoic acid  
5 benzyloxy-amide (example 1(a); 0.54 g, 1.6 mmol) was reacted with 4-  
hydroxycarbazol (0.3 g, 1.6 mmol) in the presence of potassium carbonate (0.23 g,  
1.6 mmol) in dimethyl formamide to give 8-(9H-carbazol-4-yloxy)-octanoic acid  
benzyloxyamide as an almost colorless oil (yield 0.3 g, 42%; purified by column  
10 chromatography using silica gel and ethyl acetate : heptane = 4 : 6 as eluent). MS  
(M-H<sup>+</sup>) = 429.

(b) In a manner analogous to that of example 1(c), 8-(9H-Carbazol-4-yloxy)-  
octanoic acid benzyloxyamide (300mg, 0.7 mmol) was hydrogenated in the  
presence of palladium on barium sulfate to give the title compound (110 mg) in  
46% yield as an amorphous solid. MS (M-H<sup>+</sup>) = 339.

15 Example 5

## 7-(9H-Carbazol-2-yloxy)-heptanoic acid hydroxyamide

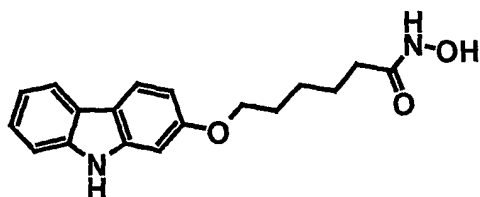
(a) In an ice bath, 2.4 ml triethylamine was added to a suspension of 2.7 g (17  
20 mmol) O-benzylhydroxylamine hydrochloride in 100 ml dichloromethane. 3.6 g  
(17 mmol) 7-bromo heptanoic acid was added, followed by 5.3 g (21 mmol) bis-(2-  
oxo-3-oxazolidinyl)-phosphorylchloride. Stirring was continued at ambient  
temperature for 18 h. The solution was extracted twice with 150 ml each of 1M

aqueous hydrochloric acid and twice with 150 ml each of 1M aqueous sodium bicarbonate. The organic solvent was removed i. vac. and the residue was purified by column chromatography (silica gel; ethyl acetate : heptane 1:1) to give 1.55 g (30%) of 7-bromo-heptanoic acid benzyloxy-amide as a colorless oil. MS: 314 ( $M+H^+$ ).

(b) In a manner analogous to that of example 1(b), 7-bromo-heptanoic acid benzyloxy-amide (1.8 g, 5.7 mmol) was reacted with 2-hydroxycarbazole (1.05 g, 5.7 mmol) in the presence of potassium carbonate (1.2 g, 8.6 mmol) in dimethyl formamide to give 7-(9H-carbazol-2-yloxy)-heptanoic acid benzyloxyamide as an almost colorless wax (yield 0.53 g, 22%; purified by column chromatography using silica gel and ethyl acetate : heptane = 4:6 to 6:4 as an eluent). MS ( $M-H^+$ ) = 415.

(b) In a manner analogous to that of example 1(c), 7-(9H-carbazol-2-yloxy)-heptanoic acid benzyloxyamide (530 mg, 1.3 mmol) was hydrogenated to give the title compound in 62% yield (260 mg) as a crystalline solid. mp 198 °C. MS ( $M-H^+$ ) = 325.

#### Example 6



#### 6-(9H-Carbazol-2-yloxy)-hexanoic acid hydroxyamide

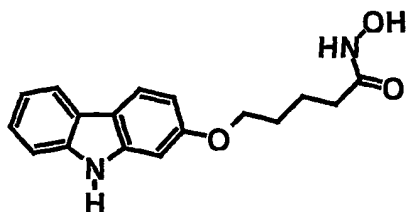
(a) 2-Hydroxycarbazole (0.5 g, 2.7 mmol), ethyl 6-bromohexanoate (0.6 g, 2.7 mmol), and potassium carbonate (0.4 g, 3.0 mmol) in dimethyl formamide (10 ml) were heated to 120 °C for 24 h. Water was added and extraction with ethyl acetate was performed. The combined organic phases were washed with water and dried (sodium sulfate). The solvent was removed i. vac. and the residue was purified by column chromatography (silica gel, ethyl acetate : heptane = 1:1) to give ethyl 6-(9H-carbazol-2-yloxy)-hexanoate (290 mg, 33%) as a colorless solid. MS ( $M-H^+$ ) 324.

(b) Ethyl 6-(9H-carbazol-2-yloxy)-hexanoate (270 mg, 0.8 mmol) and 1 N aqueous lithium hydroxide (2 ml, 2 mmol) in 15 ml methanol was heated to reflux for 1h. The solvent was removed, the residue was acidified by 1 ml 2N aqueous hydrochloric acid. The precipitate was collected to give 6-(9H-carbazol-2-yloxy)-hexanoic acid (230 mg, 93%) as a colorless solid. MS ( $M-H^+$ ) 296.

(c) 6-(9H-carbazol-2-yloxy)-hexanoic acid (220 mg, 0.74 mmol) in tetrahydrofuran (10 ml) was cooled to 0 °C. Isobutyl chloroformate (101 mg, 0.74 mmol) and N-methyl morpholine (112 mg, 1.1 mmol) was added and stirred at 0°C for 15 min.

(d) Hydroxylamine hydrochloride (77 mg, 1.1 mmol) was added to a cold (0°C) solution of potassium hydroxide (62 mg, 1.1 mmol) in methanol (2 ml). The precipitate was removed and the solution was added to a solution of the activated carboxylic acid (c). Stirring was continued for 1h at ambient temperature and the solvent was removed i.vac. The residue was purified by column chromatography (silica gel, ethal acetate : heptane 1:1) to give the title compound (53 mg, 23%) as a colorless solid. mp 192 °C. MS ( $M-H^+$ ) 311.

#### Example 7



#### 5-(9H-Carbazol-2-yloxy)-pentanoic acid hydroxyamide

(a) In a manner analogous to that of example 6(a), ethyl 5-bromo-pentanoate (685 mg, 3.28 mmol) was reacted with 2-hydroxycarbazole (600 mg, 3.28 mmol) to give ethyl 5-(9H-carbazol-2-yloxy)-pentanoate (350 mg, 34%) as a colorless solid. MS ( $M-H^+$ ) 310.

(b) In a manner analogous to that of example 6(b), ethyl 5-(9H-carbazol-2-yloxy)-pentanoate (400 mg, 1.3 mmol) was saponified to give 5-(9H-carbazol-2-yloxy)-pentanoic acid (350 mg, 96%) as a colorless solid. MS (M-H<sup>+</sup>) 282.

5 (c) In a manner analogous to that of example 6(c), 5-(9H-carbazol-2-yloxy)-pentanoic acid (350 mg, 1.2 mmol) was converted to the title compound to give 130 mg (30%) as colorless solid (MS (M-H<sup>+</sup>) 297.

### Example 8

10 In an analogous manner to that described in the examples 1-7 the following compounds are prepared:

- (a) 7-(9H-Carbazol-4-yloxy)-heptanoic acid hydroxyamide
- (b) 7-(9H-Carbazol-3-yloxy)-heptanoic acid hydroxyamide
- (c) 7-(9H-Carbazol-1-yloxy)-heptanoic acid hydroxyamide
- (d) 7-(9-Methyl-carbazol-2-yloxy)-heptanoic acid hydroxyamide
- 15 (e) 7-(9H-carbazol-2-yloxy)-5-methyl-heptanoic acid hydroxyamide
- (f) 7-(9H-carbazol-2-yloxy)-4-methyl-heptanoic acid hydroxyamide
- (g) 7-(9H-carbazol-2-yloxy)-3-methyl-heptanoic acid hydroxyamide
- (h) 7-(9H-carbazol-2-yloxy)-2-methyl-heptanoic acid hydroxyamide
- (i) 8-(9H-carbazol-2-yloxy)-2-methyl-octanoic acid hydroxyamide
- 20 (k) 7-(9H-carbazol-2-yloxy)-4-oxa-heptanoic acid hydroxyamide
- (l) 7-(9H-carbazol-2-yloxy)-3-methyl-4-oxa-heptanoic acid hydroxyamide
- (m) 7-(9H-carbazol-2-yloxy)-3-oxa-heptanoic acid hydroxyamide
- (n) 7-(9H-carbazol-2-yloxy)-3-oxa-5cis-heptenoic acid hydroxyamide
- (o) 7-(9H-carbazol-2-yloxy)-3-oxa-5trans-heptenoic acid hydroxyamide
- 25 (p) 7-(9H-carbazol-2-yloxy)-2-methyl-3-oxa-heptanoic acid hydroxyamide

**Example 9****Evaluation of inhibitory properties of the compounds of the invention**

5 To measure the inhibitory properties of the compounds of the invention, a screening assay was performed using an aminocoumarin derivative of an omega-acetylated lysine as substrate for the enzyme. This assay has been described in detail in the literature (Hoffmann, K., et al., Nucleic Acids Res. 27 (1999) 2057-2058). Using the protocol described therein, there was measured the inhibitory effect of the compounds at a concentration of 10nM. The observed inhibition rates for selected compounds are shown in the following table:

Title compound of example No.	Inhibitory effect at 10 nM in %
1	62
2	79
3	86
4	97
5	100
6	80
7	69

10

In the same assay, suberanilohydroxamic acid (SAHA), which was included as a reference, showed an inhibitory effect of 42% at 10nM.

List of References

Cancer: Principles & Practice of Oncology, Vincent T. DeVita, Jr., Samuel Hellmann, Steven A. Rosenberg; 5<sup>th</sup> Ed., Lippincott-Raven Publishers, 1997

5 DE 2208893

DE 2928483

Hoffmann, K., et al., Nucleic Acids Res. 27 (1999) 2057-2058

Koyama, Y., et al., Blood 96 (2000) 1490-1495

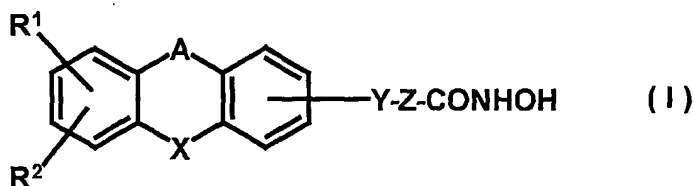
Marks, P.M., et al., Journal of the National Cancer Institute 92 (2000) 1210-1216

10 US 5,369,108

WO 98/55449

Patent Claims

## 1. Compounds of formula I



wherein

- 5        A     denotes a bond, the groups  $-\text{CH}_2-\text{O}-$ ,  $-\text{CH}_2-\text{S}-$ ,  $-\text{CH}_2-\text{CH}_2-$ , or  $-\text{NH}-\text{CO}-$ ;
- X     denotes the group  $-\text{NR}^3-$ ,  $=\text{CO}$ , or  $-\text{CH}(\text{OH})-$ ;
- Y     denotes an oxygen atom, a sulfur atom, or the group  $-\text{NR}^4-$ ;
- 10       Z     denotes a straight chain alkylene group comprising 4, 5, 6, 7, or 8 carbon atoms, wherein one  $\text{CH}_2$  group may be replaced by an oxygen or a sulfur atom, or wherein 2 carbon atoms form a  $\text{C}=\text{C}$  double bond, and which is either unsubstituted or substituted by one or two substituents selected from (1-4C)alkyl and halogen atoms;
- $\text{R}^1$  and  $\text{R}^2$  denote substituents independently selected from a hydrogen atom, halogen atoms, (1-4C)alkyl, trifluoromethyl, hydroxy, (1-4C)alkoxy, benzyloxy, (1-3C)alkylenedioxy, nitro, amino, (1-4C)alkylamino, di[(1-4C)alkyl]-amino, or (1-4C)alkanoylamino groups;
- 15        $\text{R}^3$  and  $\text{R}^4$  independently denote hydrogen atoms or (1-4C)alkyl groups;
- 20       their enantiomers, diastereoisomers, racemates and mixtures thereof.

## 2. Compounds of formula I according to claim 1

wherein

- 25       A     denotes a bond, the groups  $-\text{CH}_2-\text{O}-$ , or  $-\text{NH}-\text{CO}-$ ;
- X     denotes the group  $-\text{NR}^3-$ ,  $=\text{CO}$ , or  $-\text{CH}(\text{OH})-$ ;
- Y     denotes an oxygen atom, a sulfur atom, or the group  $-\text{NR}^4-$ ;
- Z     denotes a straight chain alkylene group comprising 4, 5, 6, 7, or 8 carbon atoms, wherein one  $\text{CH}_2$  group may be replaced by an oxygen or

a sulfur atom, or wherein 2 carbon atoms form a C=C double bond, and which is either unsubstituted or substituted by one or two substituents selected from (1-4C)alkyl and halogen atoms;

R<sup>1</sup> and R<sup>2</sup> denote substituents independently selected from halogen atoms, (1-4C)alkyl, trifluoromethyl, hydroxy, (1-4C)alkoxy, benzyloxy, (1-3C)alkylenedioxy, nitro, amino, (1-4C)alkylamino, di[(1-4C)alkyl]-amino, or (1-4C)alkanoylamino groups;

R<sup>3</sup> and R<sup>4</sup> independently denote hydrogen atoms or (1-4C)alkyl groups;

their enantiomers, diastereoisomers, racemates and mixtures thereof.

3. Compounds of formula I according to claim 1 or 2 selected from the group consisting of

8-(11-Oxo-6,11-dihydro-dibenzo[b,e]oxepin-2-yloxy)-octanoic acid hydroxyamide

rac-8-(9-Hydroxy-9H-fluoren-2-yloxy)-octanoic acid hydroxyamide

8-(9H-Carbazol-2-yloxy)-octanoic acid hydroxyamide

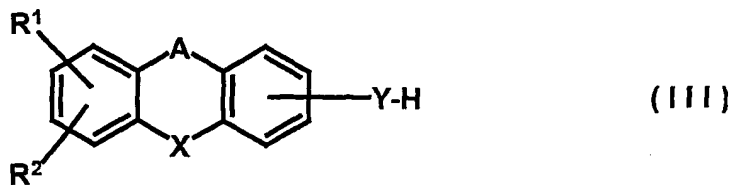
8-(9H-Carbazol-4-yloxy)-octanoic acid hydroxyamide

7-(9H-Carbazol-2-yloxy)-heptanoic acid hydroxyamide

6-(9H-Carbazol-2-yloxy)-hexanoic acid hydroxyamide

5-(9H-Carbazol-2-yloxy)-pentanoic acid hydroxyamide.

4. Process for the manufacture of compounds of formula I according to claims 1 to 3 by reacting a compound of formula III



wherein

R<sup>1</sup>, R<sup>2</sup>, A, X and Y have the above defined meaning,



- 24 -

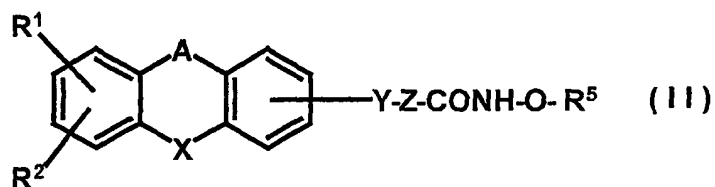
a) with a compound of formula IV



wherein

W is a displaceable group and  $R^5$  is a protecting group and Z has the meaning defined above,

to obtain a compound of formula II



wherein

$R^1$ ,  $R^2$ , A, X, Y, Z and  $R^5$  have the meaning defined above,

whereafter the protection group is split off,

or

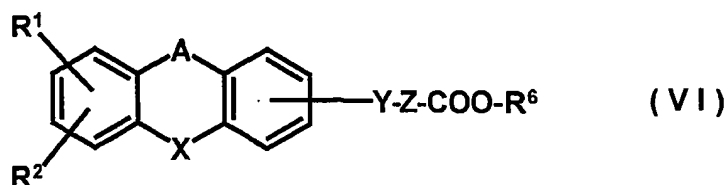
b) with a compound of formula VII



wherein

W and Z have the meaning given above and  $R^6$  is an alkyl or benzyl group, in the presence of a base,

to obtain a compound of formula VI



wherein

R<sup>1</sup>, R<sup>2</sup>, A, X, Y, Z and R<sup>6</sup> have the meaning given above,

hydrolysis of the obtained compound and reaction with hydroxylamine,

- 5 and subsequently, if desired, converting of the compound of formula I into its enantiomers or diastereoisomers.
5. Pharmaceutical compositions containing as active ingredient a compound of formula I according to claims 1 to 3 in admixture with pharmaceutically acceptable excipients or diluents.
- 10 6. Use of compound according to claims 1 to 3 for the preparation of a medicament having histone deacetylase (HDAC) inhibitor activity.
7. Use of a compound according to claim 6 as an inhibitor of cell proliferation:

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/04349

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D313/12 A61K31/335 C07C259/06 C07D209/88 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 55449 A (QUEENSLAND INST MED RES ;FAIRLIE DAVID (AU); PARSONS PETER G (AU);) 10 December 1998 (1998-12-10) cited in the application * see page 16, 45-55 *	1-7
A	US 5 369 108 A (BRESLOW RONALD ET AL) 29 November 1994 (1994-11-29) cited in the application table 1	1-7
A	WO 01 21583 A (KISHIMOTO TADAMITSU ;ONO PHARMACEUTICAL CO (JP); KONISHI MIKIO (JP) 29 March 2001 (2001-03-29) page 99	1-7
-/--		



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

8 July 2002

Date of mailing of the international search report

16/07/2002

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/04349

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 09934 A (BRIEN PATRICK MICHAEL O ;WARNER LAMBERT CO (US); PICARD JOSEPH ARM) 12 March 1998 (1998-03-12) page 34-37; claim 1 ---	1-7
A	S. HASHIMOTO: "DNA Strands Scissions by Hydroxamic acids-Copper(II) Ion under Aerobic Conditions" CHEMISTRY LETTERS, vol. 9, 1992, pages 1639-42, XP001022031 * see compound 1 * -----	1-7

## INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 02/04349

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9855449	A	10-12-1998	AU 7751698 A	21-12-1998
			WO 9855449 A1	10-12-1998
			EP 0988280 A1	29-03-2000
			JP 2002513419 T	08-05-2002
US 5369108	A	29-11-1994	AT 183185 T	15-08-1999
			AU 668696 B2	16-05-1996
			AU 2870392 A	03-05-1993
			AU 708115 B2	29-07-1999
			AU 6206396 A	17-10-1996
			CA 2120619 A1	15-04-1993
			DE 69229800 D1	16-09-1999
			DE 69229800 T2	27-04-2000
			EP 0642509 A1	15-03-1995
			ES 2134815 T3	16-10-1999
			FI 941537 A	31-05-1994
			HU 67421 A2	28-04-1995
			JP 7502494 T	16-03-1995
			KR 263264 B1	01-08-2000
			KR 258680 B1	15-05-2000
			NO 941166 A	30-05-1994
			RU 2128643 C1	10-04-1999
			WO 9307148 A1	15-04-1993
			US 5932616 A	03-08-1999
			US 5700811 A	23-12-1997
			US 6087367 A	11-07-2000
WO 0121583	A	29-03-2001	AU 7320100 A	24-04-2001
			EP 1215203 A1	19-06-2002
			WO 0121583 A1	29-03-2001
			JP 2002080445 A	19-03-2002
WO 9809934	A	12-03-1998	AU 735013 B2	28-06-2001
			AU 4159597 A	26-03-1998
			BR 9711988 A	24-08-1999
			CA 2256716 A1	12-03-1998
			EP 0931045 A1	28-07-1999
			JP 2000517341 T	26-12-2000
			NZ 333063 A	22-12-2000
			WO 9809934 A1	12-03-1998